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Co-precipitation of mefenamic acid–polyvinylpyrrolidone K30 composites using Gas Anti-Solvent

Peerapan Dittanet[a], Sasiwimon Phothipanyakun[a], Manop Charoenchaitrakool[a,b,*]

[a] Department of Chemical Engineering, Faculty of Engineering, Kasetsart University, Bangkok 10900, Thailand
[b] Center for Advanced Studies in Nanotechnology and Its Applications in Chemical, Food and Agricultural Industries, Kasetsart University, Bangkok 10900, Thailand

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ABSTRACT

In this study, composites of mefenamic acid (MEF) and polyvinylpyrrolidone K30 (PVP K30, MW ~ 40,000) were synthesized by applying the Gas Anti-Solvent (GAS) technique. It was found that an increase in drug-to-polymer ratio resulted in a higher % drug content. However, temperature and solution concentration had no significant effect on the % drug content when the amount of polymer in the solution was lower than or equal to that of the drug. The dissolution rate of the MEF–PVP composites was found to be 7 times and 3 times greater than those of the unprocessed MEF and physical mixture, respectively.

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1. Introduction

Mefenamic acid (MEF) is a non-steroidal anti-inflammatory drug that is widely used as a painkiller and inhibitor of prostaglandin synthetase [1]. According to the Biopharmaceutical Classification System (BCS), mefenamic acid can be classified as a class-II drug, meaning that it possesses high permeability but low water solubility [2]. It is typically prescribed for oral administration, with a usual dose of 250 or 500 mg, three times daily. The solubility of mefenamic acid in water has been reported to be 20 mg/L [3]. In pharmaceutical practice, ingestion of drugs which exhibit such poor water solubility can result in low dissolution and hence low oral bioavailability [4–6]. To improve the solubility and drug effectiveness, several methods have been proposed including size reduction, the use of surfactants, modification of the physicochemical properties of the drug, and production of drug–polymer composites with water-soluble carriers [7–13].

Composites of drug and polymer are widely used due to the associated low cost materials and enhancement of bioavailability for the class of low water-soluble drugs. A drug–polymer composite can be described as a homogeneous dispersion of at least two different components, usually a hydrophilic polymer matrix and a hydrophobic drug. Water-soluble polymer matrices which are often co-precipitated with drug include polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and hydroxylpropyl methylcellulose (HPMC) [14]. Among these substances, PVP is the most widely used due to it possessing remarkable properties such as high water solubility, non-toxicity to the body and preservation of the properties and activity of the co-precipitating drug. In addition, it is essentially chemically inert, pH-stable and colorless [15,16].

Traditionally, drug–polymer composite production can be employed by various techniques including spray-drying [14], co-milling [17], solvent evaporation [18] and melt extrusion [19]. Unfortunately, there are drawbacks for certain processes. For example, high-temperature operation is required for the melt extrusion method, therefore, it is limited to drugs with low thermal sensitivity. Spray-drying and solvent evaporation can potentially leave trace amounts of toxic organic solvent in the polymer matrix [4]. To overcome the limitations of these processes, an alternative method is the Gas Anti-Solvent process (GAS) for drug–polymer composite production. For the GAS process, carbon dioxide (CO_2) is commonly employed as an anti-solvent because it is easy to handle, non-toxic, has low environmental impact and is in abundant supply [4,17,20]. In addition, CO_2 has a mild critical temperature and a low critical pressure, which makes it suitable to precipitate heat-sensitive drugs. To date, there is no report on the production of MEF and PVP composites using the GAS process.

In this work, the GAS technique was employed to produce mefenamic acid–PVP composites in order to enhance the drug dissolution rate. Acetone and ethanol in a ratio of 50:50 by volume were used as organic solvent to dissolve both drug and polymer. The effects of drug concentration, drug-to-polymer ratio and

* Corresponding author. Tel.: +66 2 797 0999x1216; fax: +66 2 561 4621.
E-mail address: manop.c@ku.ac.th (M. Charoenchaitrakool).

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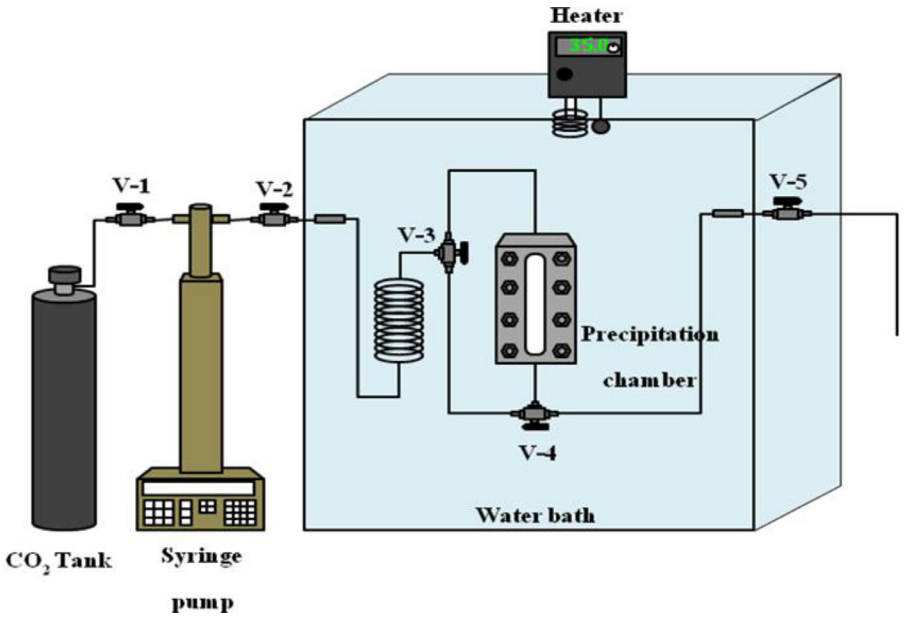

Fig. 1. Schematic diagram of the GAS process.

co-precipitation temperature on % drug content, shape and size of the composites were investigated.

2. Experimental

2.1. Materials

Mefenamic acid (Sigma Aldrich, 96.0% purity) and polyvinylpyrrolidone (PVP) with a molecular weight of 45,000 g/mole (Fluka, 99.9% purity) were used as received. Acetone (Carlo Erba Reagents, 99.8% purity) and ethanol (Carlo Erba Reagents, 99.5% purity) were used as organic solvents. The organic solvent was prepared by mixing acetone and ethanol at the ratio of 50:50 by volume. High-purity-grade carbon dioxide (TIG) was employed as an anti-solvent. Potassium phosphate monobasic (Carlo Erba Reagents, 99% purity), sodium hydroxide (Sigma Aldrich, 98% purity) and methanol (Carlo Erba Reagents, 99.5% purity) were used to prepare the phosphate buffer solution for the dissolution studies. All chemicals and reagents were used without further purification.

2.2. Precipitation of mefenamic acid–PVP composites by the GAS process

The schematic diagram of the GAS process for the production of drug–polymer composites is shown in Fig. 1. Mefenamic acid and PVP K30 were dissolved in a solvent mixture of acetone and ethanol to obtain a homogenous solution. Subsequently, 5 mL of the drug–polymer solution was injected into the precipitation chamber (Jerguson sight gauge series no. 32). The system was immersed in a water bath in which the operating system temperature was controlled to within 0.1°C using a recirculation heater (Thermoline Unistat 130). Liquid CO_2 was fed to a syringe pump (ISCO model 260D) and delivered through a preheating coil, which was immersed in the water bath. The precipitation chamber was then brought to the desired pressure by passing CO_2 from the pump through a 0.5 μm filter from the bottom. The rate of pressurization was set at 10 mL/min, and the pressure of the system was increased up to 90 bar in order to ensure a complete precipitation. Precipitated samples were then washed with CO_2 at 90 bar, using approximately 80 mL of CO_2 to remove residual solvent. After washing, the system was depressurized, and samples were removed from the precipitation chamber and taken for further analyses.

2.3. Particle characterization

The crystallinity and melting point of the unprocessed drug, unprocessed PVP and the obtained composites were tested by X-ray diffraction (XRD) (BRUKER, model D8 Discover) and differential scanning calorimetry (DSC) (TA instruments, SDT 2960). The morphology of particles was analyzed by scanning electron microscopy (SEM) (FEI, model Quanta 450). Samples were coated with gold using a sputter coater prior to analysis.

2.4. Analysis of drug content in composites

Precipitated samples of known weight were dissolved in the phosphate buffer solution containing 4% methanol by volume at a pH of 7.6. The obtained solution was then examined using a UV spectrophotometer (Shimadzu, Anthelie advance 5) at a wavelength of 285 nm for light absorption. The calibration curve for light absorbance and sample concentration was plotted and used to determine the percentage drug content of the composite. The % drug content was calculated as follows:

$$\%\,drug\ content = \frac{mass\ of\ the\ drug\ in\ particles}{total\ mass\ of\ particles} \times 100\%$$

2.5. Dissolution studies

Powder dissolution studies were performed at a pH of 7.6 and at 37 °C using a magnetic stirrer (200 rpm) in 900 mL of phosphate buffer solution containing 4% methanol by volume. Accurately weighed samples (containing 20 mg of drug) were introduced into the dissolution medium. Aliquots (≈ 4 mL) were withdrawn at certain time intervals and passed through a 0.45 μm filter. The amount of MEF in the withdrawn samples was determined by measuring the absorbance at $\lambda = 285$ nm using a UV spectrometer.

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